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Note

Synthesis of some new phenothiazinothiadiazoles and their azetidinones: Antifungal agents

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A series of 2-arylideneamino-5-(N^{10}-phenothiazinomethyl)-1,3,4-thiadiazoles **4a-k** have been synthesised via conden-sation of 2-amino-5-(N^{10}-phenothiazinomethyl)-1,3,4-thia-diazole **3** with various carbonyl compounds. Cyclo-addition of acetyl chloride to **4** gives 1-[5′-(N^{10}-phenothiazino-methyl)-1′,3′,4′-thiadiazol-2′-yl]-4-substituted-2-azetidinones **5**. Com-pounds **4** and **5** have been screened for their antifunngal activity.

Phenothiazine derivatives are known to possess various biological activities[1-5]. However, substitution at positon-10 enhances the activity of phenothiazine nucleus[6]. Phenothiazinoazetidinones[7,8] and thiadiazolylazetidinones[9] are reported as potential antimicrobil agents. Herein, we report the synthesis of several new phenothiazinothiadiazoles **4** and phenothiazinothiadiazolylazetidinones **5** and their antifungal activity.

Reaction of ethyl chloroacetate with phenothiazine yielded ethyl N^{10}-phenothiazino-acetate **1** which on reaction with thiosemicarbazide resulted in the formation of N^{10}-phenothiazinoacetylthiosemicarbazide **2**. Compound **2** on dehydrative annulation by conc H_2SO_4 afforded the thiadiazole **3** which on condensation with various carbonyl compounds furnished 2-arylidene amino-5-(N^{10}-phenothiazinomethyl)-1,3,4-thiadiazoles **4a-k**. The β-lactam moiety was introduced in compounds **4** by the cycloaddition of acetyl chloride[10,11] in the presence of base (Et_3N) in dioxane to yield 1-[5′(N^{10}-phenothiazinomethyl)-1′,3′ ,4′-thiadiazol-2′-yl-]-4-substituted-2-azetidin-ones **5a-k** (Scheme I). Purity of the compounds was monitored by TLC and the structures of the compounds were deduced on the basis of their elemental and spectral analyses (Table I).

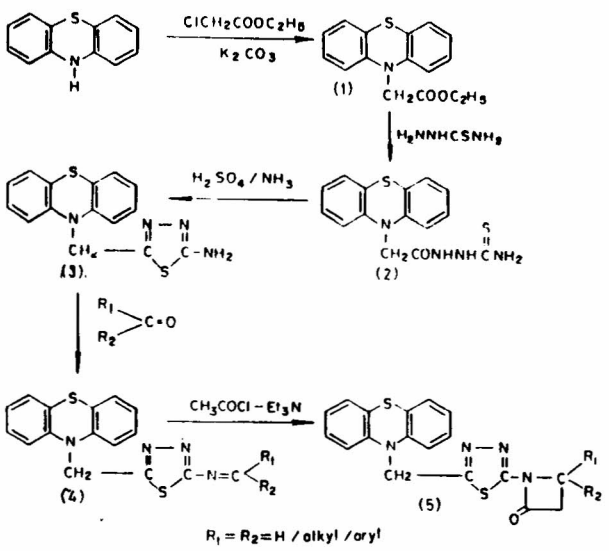
Antifungal Activity

Compounds **4** and **5** were screened for their antifungal activity against the fungi *Candida albicans, Rizopus oryzae* and *Crysosporium pannical* by the Paper disc method at 100 and 500 ppm concentrations. A commercial fungicide Griseofulvin was also tested under similar conditions for comparison. Results are presented in Table II.

The fungicidal data (Table II) indicate that all the compounds are moderately to highly toxic to the test fungi at 500 ppm concentration. The toxicity of the compound depends upon the nature and position of the substituent at the aryl moiety. Compounds **4d**, **4g**, **4k**, and **5k** displayed promising antifungal activity. Introduction of azetidinyl moiety at azomethine group diminishes the fungitoxicity of the compounds.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Beckman Acculab-10 spectrophotometer (μ_{max} in cm^{-1} and ^1H NMR spectra on a Perkin-Elmer R-32 spectrometer (90MHz, chemical shift in δ, ppm) using TMS as internal standard.



Scheme I

Table I — Characterization data of the compounds **4** and **5**.

Compd	R_1	R_2	Yield (%)	m.p °C	Mol. formula	Found (%) (Calcd) C	H	N
4b	H	4-$OCH_3C_6H_4$	79	136-7	$C_{23}H_{18}N_4OS_2$	64.09 (64.19	4.20 4.19	13.10 13.02)
4c	H	-CH=CHC_6H_5	81	141-2	$C_{24}H_{18}N_4S_2$	67.72 (67.61	4.32 4.23	13.21 13.15)
4d	H	2-ClC_6H_4	78	263-5	$C_{22}H_{15}N_4S_2Cl$	60.91 (60.77	3.52 3.45	13.01 12.89)
4e	H	4-ClC_6H_4	72	164-5	$C_{22}H_{15}N_4S_2Cl$	60.82 (60.77	3.60 3.45	12.81 12.89)
4f	H	4-$N(CH_3)_2C_6H_4$	82	101-3	$C_{24}H_{21}N_5S_2$	64.86 (65.01	4.80 4.74	15.69 15.80)
4g	H	C_4H_3O(2-furyl)	73	103-4 (d)	$C_{20}H_{14}N_4OS_2$	61.72 (61.54	3.71 3.59	14.21 14.36)
4h	H	2-OHC_6H_4	76	126-7	$C_{22}H_{16}N_4OS_2$	63.71 (63.46	3.71 3.85	13.41 13.46)
4i	CH_3	C_6H_5	79	102-4 (d)	$C_{23}H_{18}N_4S_2$	66.61 (66.67	4.38 4.35	13.66 13.53)
4j	CH_3	2-OHC_6H_4	74	124-5	$C_{23}H_{18}N_4S_2$	63.99 (64.19	4.17 4.19	12.89 13.02)
4k	C_6H_5	C_6H_5	84	091-2	$C_{28}H_{20}N_4OS_2$	70.71 (70.59	4.22 4.20	11.86 11.77)
5b	H	4-$OCH_3.C_6H_4$	80	201-2	$C_{25}H_{20}N_4O_2S_2$	63.88 (63.56	4.20 4.24	11.71 11.86)
5c	H	-CH=CHC_6H_5	78	207-8	$C_{26}H_{20}N_4OS_2$	66.90 (66.67	4.21 4.27	12.08 11.97)
5d	H	2-ClC_6H_4	74	136-7	$C_{24}H_{17}N_4OS_2Cl$	60.31 (60.44	3.54 3.57	11.71 11.75)
5e	H	4-ClC_6H_4	67	081-2 (d)	$C_{24}H_{17}N_4OS_2Cl$	60.56 (60.44	3.86 3.78	11.94 11.75)
5f	H	4-$N(CH)_3C_6H_4$	75	201-3 (d)	$C_{26}H_{23}N_5OS_2$	24.37 (24.30	4.86 4.74	14.58 14.43)
5g	H	C_4H_3O	62	106-8 (d)	$C_{22}H_{16}N_4C_2S_2$	60.89 (61.11	3.56 3.70	13.11 12.96)
5h	H	2-OHC_6H_4	69	188-9	$C_{24}H_{18}N_4O_2S_2$	63.12 (62.88	4.92 3.93	12.37 12.23)
5i	CH_3	C_6H_5	79	177-8	$C_{25}H_{20}N_4OS_2$	66.06 (65.79	4.41 4.39	12.37 12.28)
5j	CH_3	2-OHC_6H_4	74	107-8	$C_{25}H_{20}N_4O_2S_2$	65.90 (65.56	4.21 4.24	11.99 11.86)
5k	C_6H_5	C_6H_5	78	106 (d)	$C_{30}H_{22}N_4OS_2$	69.89 (69.50	4.22 4.17	10.40 10.81)

Ethyl N^{10}-phenothiazinoacetate, 1:A mixture of phenothiazine (0.1 mole), ethyl chloroacetate (0.1 mole) and anhydrous K_2CO_3(5.0 g) in acetone (80mL) was refluxed for about 15 hr on a steam-bath. The acetone was distilled off under reduced pressure and the resulting solid mass poured into water, filtered and the separated solid recrystallised from ethanol to furnish cream coloured crystals of **1**, yield 88%, m.p. 203-4°; Anal. Found: C, 67.25; H, 5.32; N, 4.85; Calcd for $C_{16}H_{15}NO_2S$: C, 67.37; H, 5.26; N, 4.91%; IR: 1735-40(>CO); ^{1}H NMR($CDCl_3$): 3.65(s, 2H, N-CH_2-), 4.20(q, 2H, *J*=7Hz,$COOCH_2$-), 1.25(t, 3H, *J*=7 Hz, CH_3) and 7.25-7.80(m, 8H, Ar-H); M^+285

Table II — Antifungal activity data* of compounds **4** and **5**.

Compd	*C.pannical*		*C.albicans*		*R.oryzae*	
	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm
4a	++	+	+++	++	++	+
4b	++	+	++	+	+	+
4c	+++	++	+++	++	+++	++
4d	+++	++	++++	+++	++++	++
4e	+	++	+++	++	+++	+
4f	++	+	++++	++	+++	++
4g	++++	+++	++++	++	++	++
4h	++	+	+++	++	+++	+
4i	++	+	+++	++	+	+
4j	+++	++	++	+	+++	++
4k	++++	+++	++++	++	+++	+
5a	++	+	+++	+	++	+
5b	++	+	++	-	+	-
5c	+++	+	+++	+	++	-
5d	+++	++	+++	++	+++	+
5e	+++	+	+++	++	+++	+
5f	++	+	+++	+	+++	+
5g	++	+	+++	+	++	+
5h	++	+	++	+	++	-
5i	+++	++	+++	+	++	-
5j	+++	++	+++	+	+++	++
5k	++++	++	+++	++	+++	++
Gf	++++	+++	++++	+++	++++	++

Gf: Griseofulvin.

* Inhibition diameter in mm. (-), 11 mm; (+), 11-14 mm; (++), 15-18 mm; (+++), 19-22 mm and (++++) 23-25 mm.

1-(N^{10}-Phenothiazinoacetyl)thiosemicarbazide, 2: Phenothiazine ester **1** (0.075 mole) and thiosemicarbazide (0.075 mole) in methanol (50 mL) was refluxed on a steam-bath for about 8 hr. The excess of the solvent was removed under reduced pressure and the viscous mass poured into ice cold water, filtered, and recrystallised from ethanol to give yellow leaflets of **2**, yield 81%, m.p. 161-62°; Anal. Found: C,54.32; H, 4.20; N,16.72. Calcd for $C_{15}H_{14}N_4OS_2$: C, 54.55; H, 4.24; N, 16.97%; IR: 3340 (-NH NH_2), 1675(-CONH) and 1135(>C=S); ^{1}H NMR ($CDCl_3$: 3.90(s, 2H, -N-CH_2-), 8.30 (m, 4H, -NHNH-CS-NH_2) and 7.10-7.50 (m, 8H, Ar-H); M^+330..

2-Amino-5-(N^{10}-phenothiazinomethyl)-1,3,4-thiadiazole, 3:A mixture of thiosemicarbazide **2** (0.05 mole) and conc. H_2SO_4 (15 mL) was kept overnight at room temperature, poured into ice cold water, neutrallised with liq. Ammonia and filtered. The product obtained was recrystallised from methanol to get **3** as greenish coloured compound, yield 86%, m.p. 116-18°; Anal. Found: C, 57.62; H, 3.80; N, 17.81. Calcd for $C_{15}H_{12}N_4S_2$: C, 57.69; H, 3.85; N, 17.95%; IR: 3355(-NH_2), 1590 (-C =N-) and 715(-C-S-C-); ^{1}H NMR ($CDCl_3$): 3.80 (s, 2H, -N-CH_2), 8.20 (s, 2H, NH_2) and 7.20-7.60 (m, 8H, Ar-H); M^+312

2-Benzylidenylamino-5-(N^{10}-phenothiazinomethyl)-1,3,4-thiadiazole, 4a: Compound **3** (25.0 m mole), benzaldehyde (25.0 m mole) and glacial acetic acid (5.0 mL) were refluxed in methanol (50 mL) for about 6 hr. The solventt was distilled off under reduced pressure and the viscous mass recrystallised from benzenechloroform to give **4a**, yield 76%, m.p. 126-27°; Anal. Found: C, 65.82; H, 3.96; N, 13.96. Calcd for $C_{22}H_{16}N_4S_2$ requires: C, 66.00; H, 4.00; N, 14.00%; IR: 1610(C=N), 1580(-N=CH-) and 700(C-S-C); ^{1}H NMR ($CDCl_3$): 3.60 (s, 2H, -N-CH_2), 4.80 (s, 1H, -N=CH-) and 7.20-7.60 (m, 11H, Ar-H); M^+, 400.

Other compounds **4b-k** were synthesised similarly using various carbonyl compounds. Their characterization data are presented in Table I.

1-[5′-(N^{10}-Phenothiazinomethyl)-1′, 3′, 4′,-thiadiazol-2′-yl-]-4-phenyl-2-azetidinone, 5a: To a stirred solution of compound **4a** (5.0 m mole) and Et_3N (10.0 m mole) in dioxane (40 mL),

acetyl chloride (10.0 m mol) was added dropwise at 0-5°. The reaction mixture was stirred for about 5 hr and the precipitated amine hydrochloride filtered off. The filtrate was concentrated under reduced pressure and poured into ice cold water. The product **5a** so obtained was recrystallised from methanol, yield 76%, m.p. 176-77°; Anal. Found: C, 65.01; H, 3.97; N, 112.86. Calcd for $C_{24}H_{18}N_4OS_2$: C, 65.16; H, 4.07; N, 12.67%; IR: 1750(>CO), 1600 (-C=N-) and 700 (-C-S-C); ^{1}H NMR (DMSO-d_6): 3.90 (s, 2H, -N-CH_2-), 3.60 (d, 2H, J = 9Hz, -CH_2-), 4.10 (d, 1H, J = 7Hz, -CH) and 7.15-7.55 (m, 13H, Ar, H); M^+, 442.

Other compounds **5b-k** were synthesised similarly. Their characterization data are presented in Table I.

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